

WHAT IS CLAIMED IS:

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1. An isolated DNA molecule, comprising a kidney-specific promoter operably linked to a heterologous DNA sequence encoding a heterologous polypeptide containing a non-native apical surface membrane targeting sequence, wherein said kidney-specific promoter is capable of driving the expression of said heterologous polypeptide *in vivo* in the kidneys to produce a recombinant biologically active polypeptide in the urine.
  2. An isolated DNA molecule according to claim 1, wherein said kidney-specific promoter is a uromodulin promoter.
  3. An isolated DNA according to claim 2, wherein said uromodulin promoter is a goat uromodulin promoter.
  4. An isolated DNA according to claim 3, wherein said goat uromodulin promoter has the nucleotide sequence of SEQ ID NO:37, or a fragment thereof capable of directing kidney-specific expression.
  5. An isolated DNA according to claim 2, wherein said uromodulin promoter is the mouse uromodulin promoter.
  6. An isolated DNA molecule according to claim 5, wherein said mouse uromodulin promoter has the nucleotide sequence of SEQ ID NO:1, or a fragment thereof capable of directing kidney-specific expression.
  7. An isolated DNA molecule according to claim 1, wherein said non-native apical surface membrane targeting

sequence is a C-terminal glycosyl phosphatidylinositol (GPI) signal sequence.

8. An isolated DNA molecule according to claim 1, wherein said apical surface membrane targeting sequence is one or more non-native sites for glycosylation at predicted  $\beta$ -turns of said heterologous polypeptide.

9. An isolated DNA molecule according to claim 8, wherein said one or more non-native sites for glycosylation are sites for Asn-linked glycosylation.

10. An isolated DNA molecule according to claim 8, wherein said one or more non-native sites for glycosylation are sites for O-glycosylation.

11. An isolated DNA according to claim 1, further comprising a secretion signal sequence operably linked to said heterologous DNA sequence.

12. An isolated DNA molecule according to claim 1, wherein said heterologous polypeptide is a fusion polypeptide.

13. An isolated DNA molecule according to claim 9, wherein said fusion polypeptide is a fusion between a heterologous polypeptide of interest and uromodulin via a chemically or enzymatically cleavable linker, said uromodulin having a GPI signal sequence at its C-terminus.

14. An isolated DNA molecule according to claim 13, wherein said linker is a protease-sensitive linker.

15. An isolated DNA molecule according to claim 1, further comprising a DNA sequence encoding phosphatidylinositol-specific phospholipase C (PIPLC), wherein said DNA sequence is disposed 3' of said heterologous DNA

sequence and is operably linked to said kidney-specific promoter, whereby said kidney-specific promoter is capable of driving the expression of said DNA sequence encoding PIPLC.

16. An isolated DNA molecule according to claim 1, wherein any basolateral surface membrane targeting signals native to said heterologous polypeptide is inactivated or deleted.

17. An isolated DNA molecule according to claim 1, further comprising a self-replicable vector.

18. A host cell transformed with the DNA molecule of claim 1.

19. A method for producing a recombinant biologically active polypeptide, comprising:

introducing the isolated DNA molecule of claim 1 into a fertilized embryo of a non-human mammal to generate a transgenic non-human mammal which expresses and secretes the heterologous polypeptide into the urine of the transgenic non-human mammal as a recombinant biologically active polypeptide;

collecting urine from the transgenic non-human mammal; and

recovering the secreted polypeptide to produce a recombinant biologically active polypeptide.

20. A method according to claim 19, wherein said introducing step comprises injecting the isolated DNA molecule into a pronucleus of a fertilized embryo.

21. A method according to claim 19, wherein the isolated DNA comprises a uromodulin promoter operably linked to a heterologous DNA sequence.

22. A method according to claim 21, wherein the uromodulin promoter is a mouse, goat, bovine or rat uromodulin promoter.

23. A method according to claim 21, wherein the uromodulin promoter is a goat uromodulin promoter.

24. A method according to claim 19, wherein said non-human mammal is a goat, cow, sheep, pig or horse.

25. A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant construct corresponding to the DNA molecule of claim 1, said DNA molecule having been introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, and wherein said mammal produces recoverable amounts of a recombinant biologically active polypeptide in its urine.

26. A transgenic non-human mammal according to claim 25 which is a transgenic goat, cow, sheep, pig or horse.

27. A transgenic non-human mammal according to claim 25, which is a transgenic goat.

28. A transgenic non-human mammal according to claim 25, in which all germ cells and somatic cells further contains a recombinant construct comprising a kidney-specific promoter operably linked to a DNA sequence encoding PIPLC, wherein said kidney-specific promoter expresses PIPLC in the kidneys of said transgenic mammal.

Sub 29. An isolated DNA molecule, comprising a kidney-specific promoter operably linked to a heterologous DNA sequence encoding a heterologous polypeptide in which

basolateral surface membrane targeting signals are inactivated or deleted.

30. An isolated DNA molecule according to claim 29, wherein said kidney-specific promoter is a uromodulin promoter.

31. An isolated DNA according to claim 30, wherein said uromodulin promoter is a goat uromodulin promoter.

32. An isolated DNA according to claim 31, wherein said goat uromodulin promoter has the nucleotide sequence of SEQ ID NO:37, or a fragment thereof capable of directing kidney-specific expression.

33. An isolated DNA according to claim 30, wherein said uromodulin promoter is the mouse uromodulin promoter.

34. An isolated DNA molecule according to claim 33, wherein said mouse uromodulin promoter has the nucleotide sequence of SEQ ID NO:1, or a fragment thereof capable of directing kidney-specific expression.

35. An isolated DNA according to claim 29, further comprising a secretion signal sequence operably linked to said heterologous DNA sequence.

36. An isolated DNA molecule according to claim 29, further comprising a self-replicable vector.

37. A host cell transformed with the DNA molecule of claim 29.

38. A method for producing a recombinant biologically active polypeptide, comprising:

introducing the isolated DNA molecule of claim 29, into a fertilized embryo of a non-human mammal to generate a

transgenic non-human mammal which expresses and secretes the heterologous polypeptide into the urine of the transgenic non-human mammal as a recombinant biologically active polypeptide;

collecting urine from the transgenic non-human mammal; and

recovering the secreted polypeptide to produce a recombinant biologically active polypeptide.

39. A method according to claim 38, wherein said introducing step comprises injecting the isolated DNA molecule into a pronucleus of a fertilized embryo.

40. A method according to claim 38, wherein the isolated DNA comprises a uromodulin promoter operably linked to a heterologous DNA sequence.

41. A method according to claim 40, wherein the uromodulin promoter is a mouse, goat, bovine or rat uromodulin promoter.

42. A method according to claim 40, wherein the uromodulin promoter is a goat uromodulin promoter.

43. A method according to claim 38, wherein said non-human mammal is a goat, cow, sheep, pig or horse.

44. A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant construct corresponding to the DNA molecule of claim 29, said DNA molecule having been introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, and wherein said mammal produces recoverable amounts of a recombinant biologically active polypeptide in its urine.

45. A transgenic non-human mammal according to claim 44, which is a transgenic goat, cow, sheep, pig or horse.

46. A transgenic non-human mammal according to claim 44, which is a transgenic goat.

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